Snapshots of Science & Medicine
Xenotransplants, Activity 2
Teacher's Instructions

The Xenotransplant-Rejection Cascade

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Introduction

This activity will introduce students to the events that occur during hyperacute and acute rejection of a xenograft, such as when an organ from a baboon or pig is transplanted into a human. Many of the complex aspects of the subject have been deliberately removed. For instance, there is no direct reference to MHC I and II antigens, the specific role of T and B cells, or the nature of the complement proteins. You may want to insert these topics to tailor the activity to the level of your students. But even with simplification, the topic will likely require some classroom discussion.

You might also want to review the meaning of "species-specific antigens" and add a brief discussion of the role of the genetic similarity of donor and recipient. The closer two organisms are genetically, the more likely a transplant will be successful.

Objectives

- Understand the nature of species-specific antigens.
- Recognize the difference between hyperacute rejection through the complement system and acute rejection through cell-mediated immunity.
- Place the events involved in hyperacute rejection of a xenotransplanted organ in the proper order.
- Understand the impact of different xenograft antirejection strategies

Materials

- Copies of the handout for each student
- Scissors

Preparation

Make a copy of the handout for each student. You might want to cut the "titles" and "diagrams" out for your students ahead of time with a paper cutter. Also, you could make a reusable classroom set of the diagrams in color by printing out multiple copies on a color printer, cutting out the diagrams, and laminating them in plastic.

Procedure

Have students read the "Research in the News" article on Xenotransplantation in Snapshots as homework. After going over some of the key ideas in class, have students separate into groups of two to four. After cutting out the captions and diagrams, students should collaboratively pair the captions with the diagrams and put them in an order that makes sense for a presentation about xenotransplant rejection. (It may be possible to come up with an order other than the one listed below, although major deviation would result in a poorly organized talk.) Choose one group to present a short talk to the rest of the class, using their ordering scheme.

[This activity would also make a good extra-credit project for a motivated student. Ask the student to do the activity as homework, then present to the class.]

Snapshots of Science & Medicine
Xenotransplantation, Science Activity 2
Student Handout

The Xenotransplantation Rejection Cascade

Introduction

The human immune system is our own "personal bodyguard." Like any good defender, it must recognize "the enemy"—that wide range of viruses, bacteria, fungi, protozoa and other would-be pathogens that we encounter every day. At the same time, the immune system must be able to distinguish friend from foe. (A guard that instantly attacks anything that moves is probably not someone you'd want in your home.)

Our immune system is genetically programmed to recognize certain proteins on our cells (self) from the thousands of invading pathogens (nonself) trying to gain a foothold in our body. But how is the immune system able to differentiate between friend and foe?

Recognition of the Body's Own Cells

Cells posses unique antigenic proteins on their membranes that are like fingerprints; no two people (except identical twins) have the same protein structures in their membranes. Our immune cells see these proteins as normal or "self." But if our cells are transplanted into another person, they cause an immune reaction. T and B cells mount an all-out attack in an attempt to rid the body of these foreign proteins.

The Recognition Problem in Xenotransplants

In the case of xenotransplants (transplanting organs across species), the genetic separation between donor and recipient is even greater. Membrane-bound proteins are less similar, and the rejection of the organ is stronger, faster, and more complex. In particular, xenotransplants trigger a response called hyperacute rejection, which can destroy a transplanted organ within just a few hours.

Hyperacute rejection results from activation of a part of the immune system called the complement system, an array of proteins that circulates in the blood. When activated, the complement proteins bind together to form "membrane-attack complexes" that can poke large holes in cell membranes. The problem is that all mammals have a set of species-specific antigens on the surfaces of cells lining blood vessels. When antibodies circulating in human blood see these antigens from another species, they quickly bind onto them and activate the complement system. The membrane-attack complexes generated then destroy the blood vessels supplying the organ with nutrients. Once hyperacute rejection gets going, the organ usually doesn't survive for more than a few hours.

But even if hyperacute rejection is blocked, rejection continues at another level. The humoral (antibodies and B cells) and cellular (macrophages and T cells) arms of the immune system come into play. These components attack the transplanted organ cell by cell, and can cause the transplanted organ to fail after weeks or months.

Blocking Rejection
Scientists are exploring several strategies to short-circuit the rejection mechanisms described above.

- Genetically engineer pigs so that they don't express the species-specific antigens that activate complement and hyperacute rejection.
- Use drugs that suppress the immune system to prevent rejection. These immunosuppressive drugs, which do a pretty good job when used in human-to-human transplants, have to be used in such high doses that the transplant recipient is left open to infection.
- Induce bone marrow chimerism. This involves replacing part of the recipient's bone marrow with bone marrow from the organ donor. Immune cells from this new bone marrow will not recognize the xenograft as foreign.

None of these strategies is perfect, but scientists continue to seek ways to improve each of them. What once seemed an impossible option, xenotransplantation, is now looked at as a real possibility in responding to the growing number of people who die while waiting for a compatible human organ transplant.

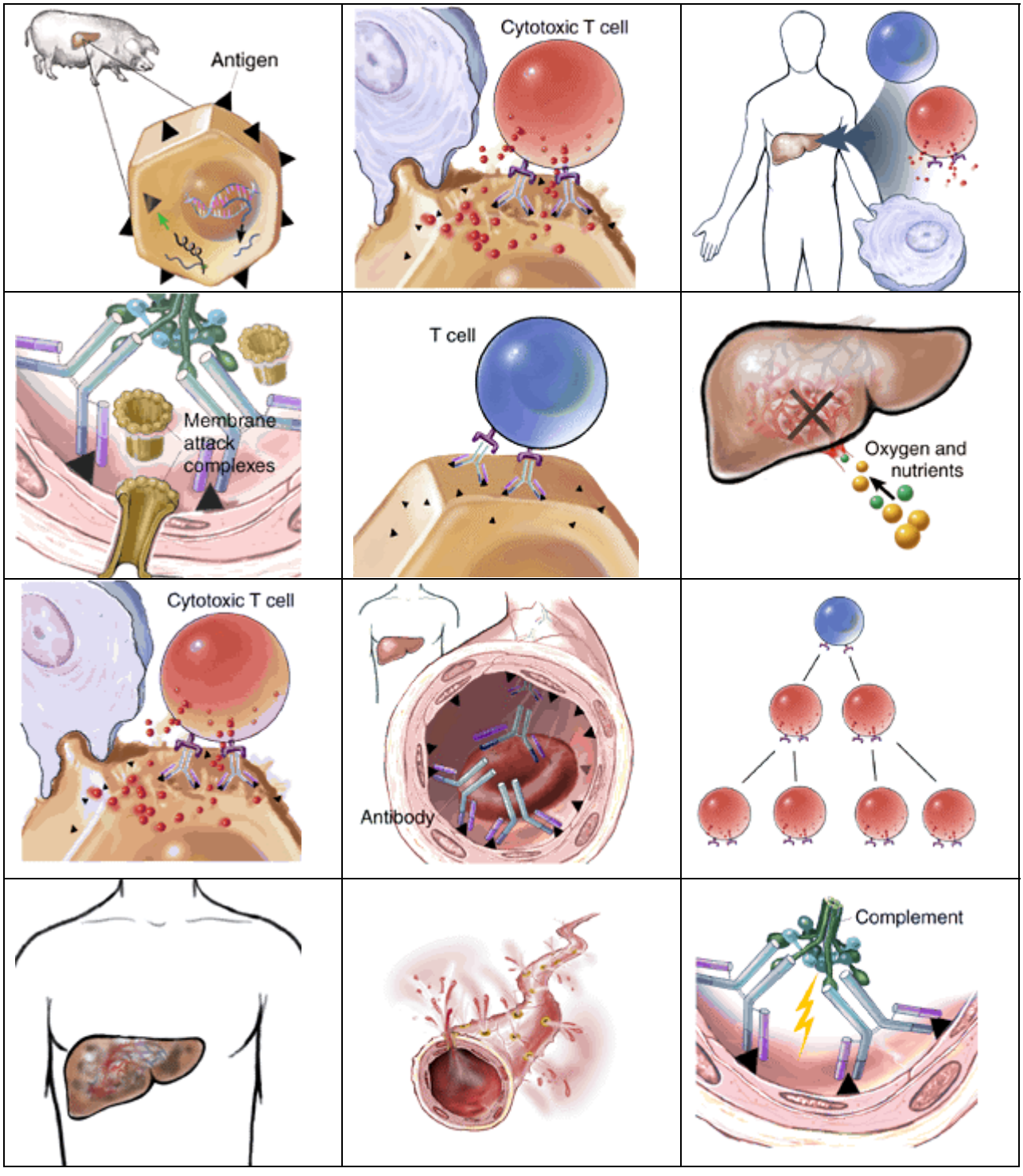
Your Challenge
Dr. Hanna Slip was on her way to your classroom to give a presentation on xenotransplant rejection and how scientists hope to avoid it. Unfortunately, a crisis intervened, and she couldn't make it (flat tire, space aliens, whatever—you decide). Fortunately, she sent her presentation slides ahead. Unfortunately, she just dropped them in a box to send them, and now they're all out of order. The attached page contains the titles of the slides, as well as a diagram for each title. Your job is to put Dr. Slip's slides back in the right order, and give the presentation in her absence.

A. Using scissors, cut out the individual slide titles and slides on the attached pages. First, pair the titles with the correct slides. Then, arrange them on your desk in an order that could be used in a presentation about xenotransplant rejection.

B. Using your correctly sequenced slides, discuss where in the rejection cascade genetic engineering of donor animals, immune-suppressing drugs, and induced bone marrow chimerism would reduce the risk of xenotransplant rejection.

Captions
Cut these out, and match them with the correct picture on the next page.

If organ somehow survives hyperacute rejection, cell-mediated rejection mechanisms still occur	Complement activation generates membrane attack complexes (protein complexes that poke holes in cell membranes)	Transport of nutrients and oxygen to the xenograft cut off
Antibodies in transplant recipient's blood bind to antigens on the cells lining the transplanted organ's capillaries.	Membrane attack complexes lyse (burst open) cells lining the capillaries of blood vessels in xenograft	T cells bind to foreign antigens on xenograft cells
Complement proteins attach to the bound antibodies, and activate	Activated T cells ignite immune response	Organ dies due lack of nutrients
Organ is damaged or dies due to cell-mediated immune attack	Pig cells display species-specific antigens on their surfaces	Cytotoxic T cells and macrophages attack xenograft cells


Antigen
Cytotoxic T cell
Membrane attack complexes
T cell
Oxygen and nutrients
Cytotoxic T cell
Antibody
Complement